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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,945	04/13/2006	Jan Bergstrom	PU0378	7078

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EXAMINER	
ZALASKY, KATHERINE M	
ART UNIT	**PAPER NUMBER**
1797	

NOTIFICATION DATE	DELIVERY MODE
09/25/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

melissa.leck@ge.com

Office Action Summary	Application No.	Applicant(s)	
	10/575,945	BERGSTROM ET AL.	
	Examiner	Art Unit	
	KATHERINE ZALASKY	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-9,11-18,20-52,54 and 55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-9 and 11-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3-9, 11-18 20-52, 54 and 55, as amended 16 December 2008, are currently pending. **Claims 16-18, 20-52, 54 and 55** are withdrawn.

In view of the appeal brief filed on 5 August 2009, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

/Vickie Kim/
Supervisory Patent Examiner, Art Unit 1797

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. **Claims 1, 3 and 5-7** are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Velander et al. (US 5,977,345).

Regarding **claim 1**, Velander et al. discloses a separation matrix comprising a porous support comprising porous particles (C10/L25-31); and ligands coupled to the surfaces of said porous support (C7/L17-21, C17/L27-33), wherein the ligands provide at least one chemical gradient in the support which said at least one chemical gradient is a continuous and smooth gradient, further wherein the chemical gradient(s) extend between the center and the exterior surface of each porous particle (C7/L17-21, C17/L27-33, Figures 4(a) and (b), C18/L32-44).

While Velander et al. does not use the exact phrase, “continuous and smooth” in the disclosure, the figures indicate that the gradient of ligand density is, in fact, continuous and smooth. Figure 4(b), for example, shows that the ligand density on the particle increases from the center of the particle to the outer radius. The figure also indicates that the reaction rate can influence the slope of the gradient on the particle.

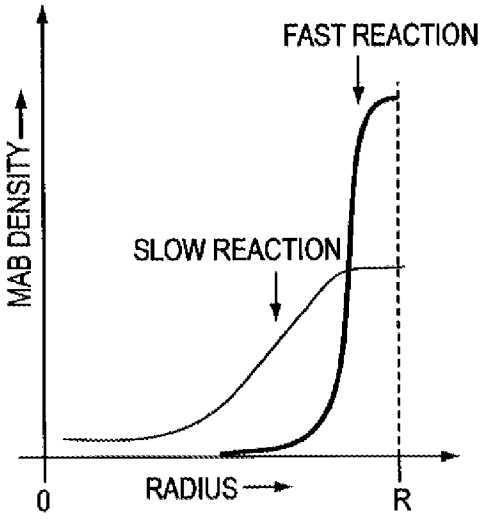


FIG. 4(B)

Therefore, as the instant specification allows for the "continuous and smooth" gradient to increase or decrease in a continuous fashion; linearly or with varying degrees of convexity or concavity, the gradient of Figure 4(b) shown in Velander et al. is "continuous and smooth".

Regarding **claim 3**, Velander et al. discloses all of the claim limitations as set forth above. Additionally, the reference discloses the separation matrix wherein at least one chemical gradient is a ligand density gradient formed by a changing density of ligands on the support (C7/L17-21, C17/L27-33, Figure 4(b)).

Regarding **claim 5**, Velander et al. discloses all of the claim limitations as set forth above. Additionally, the reference discloses the separation matrix wherein in the ligand density gradient(s), the ligand concentration increases towards the center of the support (C17/L17-33).

Regarding **claim 6**, Velander et al. discloses all of the claim limitations as set forth above. Additionally, the reference discloses the separation matrix wherein in the ligand density gradient(s), the ligand concentration decreases towards the center of the support (C2/L33-54, C17/L27-33). While the reference discloses that it is preferable to have the ligand concentration increase toward the center of the support, the reference also discloses that is conventional and well known to use an "outside-in" approach where the outer strata is activated to a higher degree than the interior (C2/L33-54).

Regarding **claim 7**, Velander et al. discloses all of the claim limitations as set forth above. Additionally, the reference discloses the separation matrix wherein the matrix is a chromatography matrix comprised of a plurality of essentially spherical particles, wherein each particle presents one or more chemical gradient(s) perpendicular to the direction of the liquid flow applied in chromatography (C10/L25-31).

Regarding limitations recited in **claim 7** which are directed to a manner of operating a chromatography column with the separation matrix, it is noted that neither the manner of operating a disclosed device nor material or article worked upon further limit an apparatus claim. Said limitations do not differentiate apparatus claims from prior art. See MPEP § 2114 and 2115. Further, it has been held that process limitations do not have patentable weight in an apparatus claim. See *Ex parte Thibault*, 164 USPQ 666, 667 (Bd. App. 1969) that states “Expressions relating the apparatus to contents thereof and to an intended operation are of no significance in determining patentability of the apparatus claim.”

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. **Claims 1, 3-9 and 11-15** are rejected under 35 U.S.C. 103(a) as being unpatentable over Bergstrom et al. (US 6,426,315) in view of Velander et al. (US 5,977,345).

Regarding **claim 1**, Bergstrom et al. discloses a separation matrix comprising a porous support comprising porous particles (C1/L6-10); and ligands coupled to the surfaces of said porous support (C3/L37-39, C4/L58-C5/L7), wherein the ligands provide at least one chemical gradient in the support (C1/L63-67), further wherein the chemical gradient(s) extend between the center and exterior surface of each porous particle (C1/L63-67).

Bergstrom et al. does not explicitly disclose the matrix wherein said at least one chemical gradient is a continuous and smooth gradient. Rather, regarding a change in ligand density, the reference discloses (C6/L17-26):

> One aspect of the invention is matrices which can be prepared according to the invention. These matrices contain one or more layers having different functionality. The substitution degree for at least one ligand from the groups 1–11 in one layer is often different from the substitution degree for the same ligand in another layer. In many embodiments of the matrices of the invention, the substitution degree of a ligand in the surface layer is zero or close to zero, while at the same time the same ligand is present in an inner layer. Also the reversed can be true.

Therefore, Bergstrom et al. teaches that the degree of substitution of ligands may be increased or decreased as one moves from layer to layer within the porous matrix. The reference does not disclose any further details of how this change in ligand density may be achieved or that this would constitute a stepwise or a continuous ligand density gradient.

Velander et al. teaches a method of activating the porous particle in such a way as to create a gradient of activated groups to which ligands may be attached (C7/L17-21, C17/L27-33, Figures 4(a) and (b), C18/L32-44). The gradient of activated groups is

changed by altering the reaction rates during ligand diffusion into the matrix (C18/L32-44). Figure (b) of Velander et al. shows how the ligand density across the particle radius changes as a function of reaction rate:

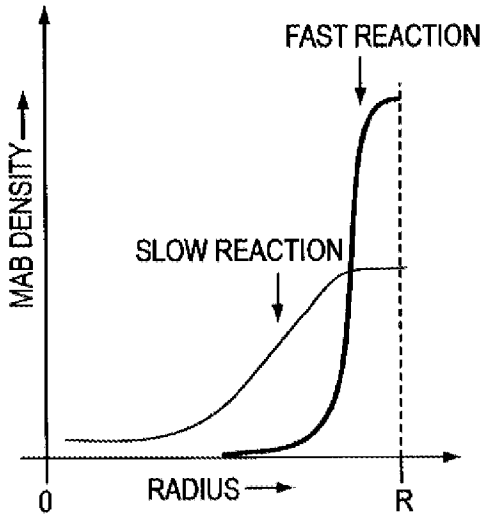


FIG. 4(B)

Finally, Velander et al. also teaches that it is beneficial to have a higher degree of activation on the interior of the particle, allowing there to be a greater concentration of ligands on the interior of the particle because the adsorptive capacity of the particle is increased (C3/L61-C4/L4, C6/L20-24, C17/L17-33). While Velander et al. does not use the exact phrase, “continuous and smooth” in the disclosure, the figures indicate that the gradient of ligand density is, in fact, continuous and smooth. Figure 4(b), for example, shows that the ligand density on the particle increases from the center of the particle to the outer radius. The figure also indicates that the reaction rate can influence the slope of the gradient on the particle. Therefore, as the instant specification allows for the "continuous and smooth” gradient to increase or decrease in a continuous

fashion; linearly or with varying degrees of convexity or concavity, the gradient of Figure 4(b) shown in Velander et al. is "continuous and smooth".

It would have been obvious to one having ordinary skill in the art at the time of the invention to use the method of inside out activation to generate a smooth and continuous ligand density gradient in the separation matrix of Bergstrom et al., as taught by Velander et al. will help increase in the adsorptive/separation capacity of the particle by allowing more access to the intra-particle region. Additionally, one of ordinary skill in the art would have been motivated to obtain the details of how to change the ligand density across the radius of a porous particle which are missing from Bergstrom et al., by performing a literature search or by reviewing known references, such as Velander et al.

Regarding **claims 3-9**, modified Bergstrom discloses all of the claim limitations as set forth above. Additionally, Bergstrom et al. discloses the separation matrix wherein:

- at least one chemical gradient is a ligand density gradient formed by a changing density of ligands on the support (C6/L17-26)
- two or more chemical gradients are present in the support and at least one gradient is a ligand density gradient (C6/L17-26, one or more layers with different functionalities, and varying the degree of substitution)
- in the ligand density gradient(s), the ligand concentration increases towards the center of the support (C6/L17-26)

- in the ligand density gradient(s), the ligand concentration decreases towards the center of the support (C6/L17-26)
- the matrix is a chromatography matrix comprised of a plurality of essentially spherical particles (C4/L20-38), wherein each particle presents one or more chemical gradient(s) perpendicular to the direction of the liquid flow applied in chromatography (C1/L63-67, the gradient on a spherical particle, therefore the gradient will extend radially and at least one gradient will exist perpendicular to an applied liquid flow)
- at least one gradient is the result of varying pKa values of functional groups of the ligands present on the support (C3/L37-39, C4/L58-C5/L7, each different ligand has a different pKa value)
- at least one chemical gradient is the result of a varying net charge of the ligands present on the support (C5/L17-24, Example 3, C10/L26-29)

Regarding limitations recited in **claim 7** which are directed to a manner of using the separation matrix, such as applying a flow of liquid in chromatography, it is noted that neither the manner of operating a disclosed device nor material or article worked upon further limit an apparatus claim. Said limitations do not differentiate apparatus claims from prior art. See MPEP § 2114 and 2115. Further, it has been held that process limitations do not have patentable weight in an apparatus claim. See *Ex parte Thibault*, 164 USPQ 666, 667 (Bd. App. 1969) that states "Expressions relating the apparatus to contents thereof and to an intended operation are of no significance in determining patentability of the apparatus claim."

Regarding **claims 5 and 6**, Velander et al. additionally discloses that in the ligand density gradient(s) the ligand concentration increases towards the center of the support (C17/L17-33). Velander et al. While the reference discloses that it is preferable to have the ligand concentration increase toward the center of the support, the reference also discloses that is conventional and well known to use an "outside-in" approach where the outer strata is activated to a higher degree than the interior (C2/L33-54, C17/L27-33).

Regarding **claims 11-15**, modified Bergstrom discloses all of the claim limitations as set forth above. Additionally, Bergstrom et al. discloses the separation matrix wherein:

- the ligands present on the porous support provide at least two different functionalities (C3/L37-39)
- said functionalities are selected from the group consisting of cation exchange ligands, anion exchange ligands, hydrophobic interaction chromatography (HIC) ligands, reversed phase chromatography (RPC) ligands, immobilized metal chelating ligands (IMAC), thiophilic ligands, and affinity ligands (C4/L58-C5/L7)
- said at least two different functionalities are present on the same ligand (C5/L25-34, ligand may be an IgG binding protein, made up of amino acids)

- the ligands present zwitterionic functionalities (C5/L25-34, ligand may be an IgG binding protein, made up of amino acids, which have zwitterionic functionalities)
- said at least two different functionalities are present on different ligand kinds, and each such ligand kind provides a separate chemical gradient within the support (C1/L63-67, C3/L37-39)

Allowable Subject Matter

7. The examiner would like to note that while the generic claim language currently in the Application is not patentable, a species of the invention may be allowable. For example, an incorporation of the type of ligand in the ligand density gradient, such as 3-mercaptopropionic acid from examples, and an incorporation of the particular composition of the porous particles will help differentiate the instant invention from the prior art.

Response to Arguments

8. Applicant's arguments filed 5 August 2009 have been fully considered but they are not persuasive.

9. To the extent that the previously filed arguments may be applied to the new grounds of rejection, with respect to Velander et al., the examiner would like to respond as follows:

The Appellant has argued that Velander et al. only teaches discrete layers of different ligand densities. However, Velander et al. very clearly shows that the severity in the slope of a ligand density gradient across the radius of a bead can be altered by

changing the reaction rate of ligand diffusion into the particle. The following figure is representative of the distribution of ligand density across the radius of the particle as a function of reaction rate:

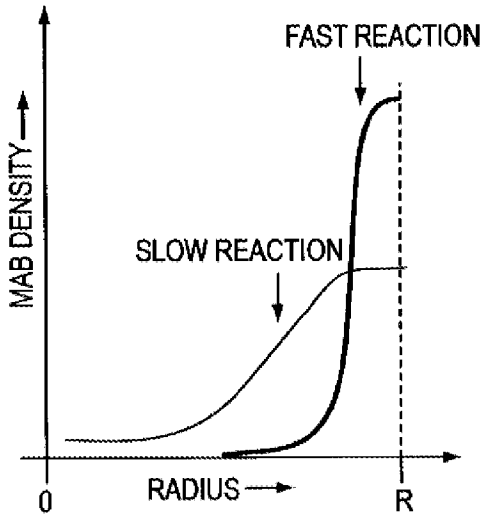
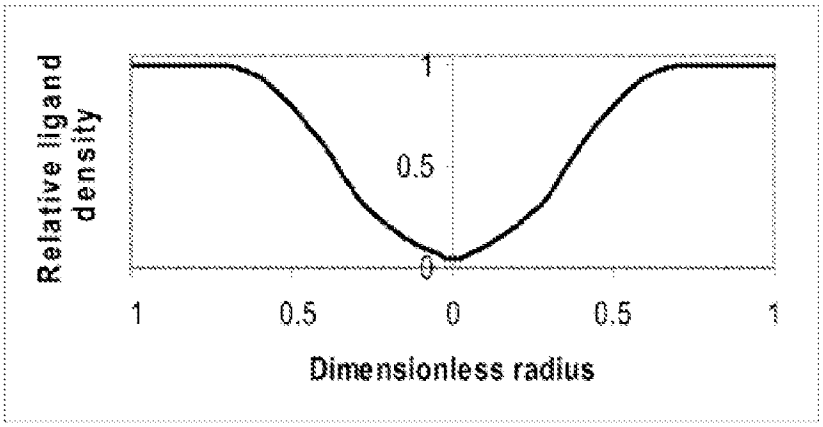


FIG. 4(B)

Further, it is noted that the idea of ligand diffusion into the porous matrix presented here in Velander et al. is the same as that presented in the instant Application as a method to achieve chemical gradients across a porous particle. The figure above shows a continuous and smooth gradient of ligand density and is not unlike the figures of the instant application which also depict ligand density as a function of the particle radius, for example, figure 7D:

Fig. 7 D



Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHERINE ZALASKY whose telephone number is (571) 270-7064. The examiner can normally be reached on Monday-Thursday, 7:30am - 6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Vickie Kim can be reached on (571)272-0579. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Krishnan S Menon/
Primary Examiner, Art Unit 1797

/KZ/
22 September 2009